New medical treatments in thyroid cancer

On behalf of the Thyroid Task Force of the BSMO

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Thyroid cancers are rare diseases and include types that range from indolent localised differentiated carcinomas to fulminant and lethal anaplastic disease. Until recently, treatment options for advanced or metastatic radio-iodine refractory thyroid cancer were limited. Recently kinase inhibitors targeting angiogenesis and other pathways have shown promising activity.

(Belg J Med Oncol 2014;8(3):81-6)

Introduction

Thyroid carcinomas are divided into different histological types.[1] Differentiated thyroid cancers (DTC) account for 90% and are subdivided into papillary (PTC), follicular (FTC) and mixed tumours. Anaplastic thyroid cancer (ATC) accounts for 1-2% and has the worst prognosis. Because of its aggressive nature, all ATC are classified as stage IV according to the American Joint Committee on Cancer (AJCC), regardless of tumour size, presence of lymph nodes or distant metastasis. Medullary thyroid cancer (MTC), which has a distinct cellular origin, accounts for approximately 5-10% and may be sporadic (75%) or hereditary (25%).

Distant metastases are the main cause of mortality and are observed in less than 10% of DTC and in 50% of MTC or ATC.

Treatment of thyroid cancer is based on surgery, both for primary and regional metastatic disease. DTC is also responsive to radioactive iodine (RAI) and thyroid hormone therapy, but ATC and MTC are not.[1]

For symptomatic or rapidly progressive advanced metastatic disease, chemotherapy treatment options are limited and mainly doxorubicin based, resulting in response rates (RR) of 25% or less in DTC and MTC.[2,3] ATC cells have been shown to be chemoresistant, but in a phase II study paclitaxel demonstrated a response rate of 53%.[4]

The present article is written by the members of the thyroid task force of the Belgian Society of Medical Oncology (BSMO) and reviews the contemporary targeted therapies for thyroid carcinoma.

Molecular biology of thyroid carcinoma

Angiogenesis

Angiogenesis, regulated by the vascular endothelial growth factor receptor (VEGFR) family and its ligands, plays an important role in tumour proliferation and metastasis. The importance of angiogenesis in thyroid cancer is supported by a number of observations: 1) a high vascularity, 2) an overexpression of VEGFR-1 and VEGFR-2 and 3) correlation of VEGF expression with risk of metastases and shorter disease-free survival.[5,6]

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: kinase inhibitors, thyroid cancer.

Table 1. Targets of different multi-targeted tyrosine kinases inhibitors.

Drug	IC_{50} (nM)						
	VEGFR-1	VEGFR-2	VEGFR-3	RET	RET/PTC3	RAF	Other targets
Sorafenib	-	90	20	49	50	6	-
Sunitinib	2	9	17	41	224	-	-
Vandetanib	1600	40	110	100	50-100	-	EGFR
Pazopanib	10	30	47	-	-	-	PDGFR, cKIT
Axitinib	1.2	0.25	0.29	-	-	-	-
Motesanib	2	3	6	59	-	-	PDGFR, cKIT
Cabozantinib	-	0.035	14	4	-	-	c-MET, cKIT
Lenvatinib	22	4	5	35	-	-	PDGFR, FGFR-1

Oncogenic kinases

Different oncogenic mutations have been recognised in all types of thyroid cancer.

In the majority of PTC activating mutations of BRAF (45%), RAS (10%) and the rearranged RET/PTC (20%) have been identified.[1] FTC develop through molecular pathways involving either RAS mutations (20-50%) or PAX8-PPARγ rearrangements (35%).[1] In ATC several mutations have been identified such as BRAF, PI3K and P53 mutations.[1] Finally in MTC, activating RET mutations are present in most familial forms and in 50% of sporadic forms.[7]

Targeted therapies in thyroid cancer

VEGFR inhibitors

VEGFR inhibitors are multi-targeted kinase inhibitors (KI), primarily targeting angiogenesis. However, given the structural similarity between RET and VEGFR, most of these molecules are capable of inhibiting both. Other targets vary between different KIs but their therapeutic significance remains unclear. *Table 1* outlines the targets for different KIs. In total 26 trials with eight different KIs have been reported in thyroid cancer (*Table 2*).

In phase II trials for DTC, RR for sorafenib ranged from 15-38%.[8-13] A randomised, placebo-controlled phase III study evaluating the efficacy of sorafenib in RAI-refractory DTC (Decision) resulted in an extended median progression free survival (PFS) by five months (10.8 versus 5.8 months, p<0.0001).[14] In ATC, the activity of sorafenib was limited: RR of 10% and median PFS two months.[15] In MTC, sorafenib demonstrated significant RR and durable SD.[8,13,16]

In phase II trials including mainly DTC, RR for sunitinib varied between 6 and 31%.[17-19] In MTC, sunitinib resulted in a partial response (PR) in 35% with a median PFS of seven months.[20]

A randomised phase II trial in DTC demonstrated significantly longer PFS for vandetanib compared to placebo (11 versus 6 months, p=0.008).[21] No difference in overall survival was observed between the two groups but a substantial number of patients receiving placebo crossed over to vandetanib. In phase II trials in MTC the RR was 16 and 20%.[22,23] In a randomised, placebo-controlled phase III trial vandetanib demonstrated significant improvement of PFS (not reached versus 19 months, p<0.01), RR (45% versus 13%, p<0.001) and disease control rate (DCR) (87% versus 71%, p=0.01).[24] Based on these results vandetanib is approved in Canada, Switzerland, Europe and the USA for the treatment of medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease and is reimbursed in Belgium since May 2013.

Treatment with cabozantinib demonstrated in DTC a PR in 53% and in MTC in 29%.[25,26] Recently, a randomised placebo-controlled phase III study in MTC (EXAM) demonstrated significant improvement of PFS (11 versus 4 months, p<0.0001) and RR (28 versus 0%, p<0.0001) for cabozantinib.[27] It is important to note that in this study documented disease progression within the past fourteen months was necessary for inclusion, while it

Table 2. Studies comparing various sequences of hormonal therapy and radiotherapy in adjuvant treatment of breast cancer.

Phase	Drug (reference)	Patients number/ Subtype	% OR	% SD > 6months	PFS (months)
III	Sorafenib[14] vs placebo	417 DTC	12 vs1	42 vs 33	11 vs 6 (p<0.0001)
	Vandetanib[24] vs placebo	331 MTC	82 vs 2	NR	Not reached vs 19 (p<0.01)
	Cabozantinib[27] vs placebo	330 MTC	28 vs 0	NR	11 vs 4 (p<0.0001)
II	Vandetanib vs placebo[23]	72 DTC	8 vs 5	NR	11 vs 6 (p=0.008)
II	Sorafenib[8-13, 15,16]	30 DTC	23	NR	NR
		41 PTC	15	56	56
		32 DTC	25	34	34
		34 DTC/MTC	15	73	73
		55 DTC	38	NR	NR
		31 DTC	31	NR	NR
		20 ATC	10	NR	NR
		16 MTC	6.3	56	56
	Sunitinib[17-20]	35 DTC/MTC	31	37	13
		43 DTC/ATC/MTC	13	NR	NR
		17 DTC/ATC/MTC	6	NR	NR
		25 MTC	35	NR	7
	Vandetanib[22,23]	30 MTC	20	53	28
		19 MTC	16	53	NR
	Cabozantinib[25]	15 DTC	53	NR	NR
	Pazopanib[28,29]	37 DTC	49	NR	NR
		16 ATC	0	NR	2
	Axitinib[30]	60 DTC/ATC/MTC	30	NR	18
	Motesanib[31,32]	93 DTC	14	35	10
		91 MTC	2	48	12
	Lenvatinib[33,34]	58 DTC	50	NR	13
		59 MTC	36	NR	9
I	Cabozantinib[26]	37 MTC	27	41	NR

OR: objective response; SD: stable disease; PFS: progression free survival; DTC: differentiated thyroid cancer; MTC: medullary thyroid cancer; ATC: Anaplastic thyroid cancer; NR: not reported.

was not in the study with vandetanib.
Other multi-targeted KI such as pazopanib, axitinib, motesanib and lenvatinib, have shown promising activity (both RR and durable SD) in open-label phase II trials, mainly in DTC and MTC.[28-34] Efficacy in ATC is often disappointing.[29,30] A phase III trial (Select) in DTC with lenvatinib completed enrolment in October 2012. The results of this trial were reported at ASCO 2014. In a press release, Eisai stated that the trial reached its primary endpoint of progression free survival benefit and that marketing authorisation applications will be submitted.

Other anti-angiogenic drugs
Fosbretabulin or combretastatin A4 phosphate (CA4P) is a vascular disrupting agent and was studied in patients with ATC. In monotherapy 27% of patients demonstrated a SD and six months OS was 34%.[35] In a randomised phase II/III trial, the addition of CA4P to carboplatin/paclitaxel chemotherapy after surgery led to a non-significant improvement of median survival (8.2 versus 4.0 months, p=0.25) and one year survival (17 versus 10%).[36]

Other targeted agents
In phase I, selective inhibitors of mutant BRAF have activity.[37,38] A phase II study with vemurafenib in BRAF mutant PTC reported objective responses in 26 and 35% for patients with or without prior treatment with a kinase inhibitor and a median PFS of seven and sixteen months respectively.[39]
Selumetinib, a MEK inhibitor, increased ^{124}I uptake in patients with RAI-refractory DTC.[40]
In addition combinations of VEGFR-inhibitors with mTOR inhibitors are currently under investigation.
In a small phase II study, Ha et al treated eleven patients with advanced ATC with imatinib, a selective inhibitor of KIT and PDGFR. Among these patients two obtained a PR and four a SD with a six month OS of 46%.[41]

Conclusion

Throughout the past years, biological discoveries and novel therapies have changed treatment options for patients with advanced thyroid cancer.
In DTC and MTC multi-targeted KIs have produced promising results, in contrast to chemotherapy previously. However, prior to initiation of KI therapy, it is important to identify which patient may benefit from such a treatment because of possible important adverse effects such as hypertension, heart failure, proteinuria, gastrointestinal events, effects on thyroid function and haematological effects. In general, patients who are candidates for treatment are patients with symptomatic disease, large tumour burden or rapid disease progression and good overall performance status. Advanced metastatic DTC and MTC without symptoms, low tumour burden and slow progression can be followed at regular time intervals every six to twelve months and do not need systemic treatment instantly. For DTC, sorafenib resulted in significant PFS improvement in a randomised phase III study and results with lenvatinib are awaited. None of the drugs are currently reimbursed for DTC, but for sorafenib, there is currently a medical need program.
For MTC, placebo-controlled phase III trials with vandetanib and cabozantinib have resulted in improvement of RR and PFS. Cross trial comparison is impossible as inclusion criteria were different. Vandetanib is reimbursed since May 2013 in Belgium, making it the first line treatment of choice for patients with advanced MTC in need of systemic treatment.
Due to the aggressiveness of the disease all patients with advanced ATC are candidates for systemic treatment. At the present time, paclitaxel appears to have some efficacy. Results with KIs were less promising but fosbretabulin alone or in combination with chemotherapy did show interesting activity. Further investigation of these and other drugs is needed in this deadly disease, including rational designed preclinical experiments based on the genomics of this cancer.
In conclusion, VEGFR inhibitors are currently becoming standard of care for advanced RAI refractory DTC and MTC. However, further research to improve outcome and overcome resistance is warranted. Inclusion of patients in clinical trials as often as possible is preferable.

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Key messages for clinical practice

1. Multi-targeted kinase inhibitors have shown promising activity in differentiated and medullary thyroid cancer, both in phase II and phase III trials.
2. For advanced differentiated and medullary thyroid cancer systemic treatment is only indicated in the case of symptomatic disease, high tumour burden or rapid disease progression.
3. For differentiated thyroid cancer, sorafenib has demonstrated significant improvement in progression free survival over placebo.
4. For medullary thyroid cancer, phase III studies with vandetanib and cabozantinib have demonstrated significant improvement in progression free survival over placebo.
5. In anaplastic thyroid cancer the medical need remains high.
6. Other targets are currently under investigation for therapeutic impact.

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